PATENT SPECIFICATION 671,023

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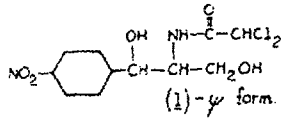
COMPLETE SPECIFICATION

Therapeutic Compositions Containing Chloramphenicol

We, PARKE, DAVIS & COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, the Foot of Joseph Campau at the River, in the City of Detroit, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Chloramphenicol is an antibiotic which can be produced by chemical synthesis or by cultivation of *Streptomyces venezuelæ* on or in a nutrient medium under aerobic conditions. Chemically it is *(l)*-ψ-1-*p*-nitrophenyl - 2 - dichloroacetamido - propane-1,3-diol and has the following structural formula.



(l)-ψ form.

Other chemical names for this product are D-(—)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol and D-*threo*-N-(1,1')-dihydroxy-1 - *p* - nitrophenylisopropyl)-dichloroacetamide.

Chloramphenicol and its optical racemate, the *(dl)*-ψ form, are of great value in the treatment of many infections and diseases which before their advent were fatal and/or resulted in long, lingering illnesses. Among such infections and diseases were typhoid fever, Malta fever, Rocky Mountain spotted fever, typhus, yaws, pneumonia, pertussis, brucellosis, urinary infections, gonorrhea, certain types of syphilis, etc. In the treatment of these ailments the customary dosage is 1—3 g. of chloramphenicol orally per day, while slightly larger quantities of the optical racemate are usually used. In many instances oral administration of these products is not possible or feasible due to the age or condition of the patient. In these and many other cases the preferred mode of administration is the parenteral route and, in particular, the intravenous route. Unfortunately, the virtual oil and water-insolubility of chloramphenicol and optically racemic chloramphenicol make it impossible to use this alternative method of administration and hence many patients have prior to the instant invention been deprived of the therapeutic effects of these valuable antibiotics.

It is an object of the present invention to produce clear solutions containing a high concentration of chloramphenicol or optically racemic chloramphenicol which are suitable for parenteral administration.

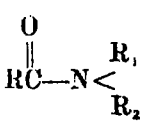
It is also an object of the present invention to provide solutions containing a high concentration of chloramphenicol or optically racemic chloramphenicol which are physically stable and from which the chloramphenicol or optically racemic chloramphenicol does not separate even on long storage.

A further object of the invention is to provide solutions containing a high concentration of chloramphenicol or optically racemic chloramphenicol which are chemically stable, that is, do not lose their therapeutic efficacy even on prolonged storage.

A still further object of the invention is to provide solutions of the above character which upon intravenous administration or upon dilution with water, normal saline, isotonic glucose solution, or plasma remain perfectly clear and do not deposit crystals of chloramphenicol or optically racemic chloramphenicol.

In accordance with the invention these and other objects which will appear hereinafter are realized by dissolving chloramphenicol or optically racemic

chloramphenicol in a water-miscible amide or an aqueous solution containing at least 30% by volume of the water-miscible amide, said amide having the formula,



where R and R_1 are the same or different and represent hydrogen or alkyl radicals containing 1 to 2 carbon atoms inclusive and R_2 is an alkyl radical containing 1 to 2 carbon atoms inclusive. In the dilute solutions, that is, those in which the solvent is not composed solely of the water-miscible amide, the balance of the solvent solution is made up of water which can contain, if desired, such things as sodium chloride, sucrose and glucose.

The solutions of the invention are chemically stable, that is, upon prolonged storage the solutions retain their titre of chloramphenicol and insofar as can be determined the water-miscible amides undergo no chemical change. The solutions are also physically stable and do not deposit crystals upon storage or on dilution with aqueous solvents such as water, normal saline, isotonic glucose solution and plasma even though in the diluted form they contain a greater concentration of chloramphenicol or its optical racemate than is obtainable in an otherwise identical solution of water, normal saline, isotonic glucose solution or plasma containing no water-miscible amide. This stability upon dilution is of extreme importance in intravenous therapy in that there is no danger of crystals of the antibiotic forming in the blood stream when using the undiluted preparations. This latter property is also of importance in that it permits dispensing chloramphenicol or its optical racemate in a concentrated form which can be diluted in case the physician desires to administer the drug by venoclysis.

The products of the invention like chloramphenicol and its optical racemate are relatively non-toxic. For example, a solution containing 25% by weight of chloramphenicol in a solvent composed of equal parts of water and N,N-dimethylacetamide has a Maximum Tolerated Dose upon intravenous administration* to albino rats of 0.767 cc./kg. and an LD_{50} of 1.109 cc./kg. Another solution having the same composition has been administered intravenously in doses of 4 cc. per day to human patients suffering from yaws. This medication was continued for a period of six days at the end of which time none of the patients showed any toxic manifestations.

The concentration of the antibiotic obtainable in the compositions of the invention varies with the amide employed and the amount of water present in the preparation. However, even when using the amides having the poorest ability to dissolve chloramphenicol (and its racemate) and a solution containing 65 to 70% water, solutions containing at least 10% by weight of the antibiotic can be prepared. In this connection it has been found that the tertiary amides, that is, those wherein R_1 is an alkyl radical, uniformly make it possible to prepare more concentrated solutions of chloramphenicol (or its racemate) than do the corresponding secondary amides wherein R_1 is hydrogen and hence the tertiary amides as a class are preferred for the purposes of this invention. Using this preferred class of amides in the anhydrous form, solutions containing about 50 to 65% by weight of chloramphenicol can be prepared. The relative concentrations of chloramphenicol obtainable using some of the above defined water-miscible amides with varying proportions of water is shown more fully in the following table.

TABLE

% by Volume of Amide in Solvent*	Milligrams of Chloroamphenicol which can be Dissolved in 1 cc. of Amide Solution					
	$HC(=O)N(CH_3)_2$	$CH_3C(=O)NHCH_3$	$CH_3C(=O)N(CH_3)_2$	$CH_3C(=O)NHC_2H_5$	$CH_3C(=O)N(C_2H_5)_2$	$CH_3CH_2C(=O)N(CH_3)_2$
(pure amide) 100%	>1333	1000	>13333	>800	>870	>1000
85%				>670	>600	
75%	>1000	560	>1000	>600		
67%		420				
60%	>800		>800	330	540	
50%	500		500	182	440	500
40%	275		280		250	
(pure water) 0%	3	3	3	3	3	3

* Balance of 100% made up with distilled water.

The invention is illustrated further by the following examples.

EXAMPLE 1.

25 g. of chloramphenicol is added to 80 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl acetamide and distilled water at room temperature and the mixture stirred or shaken until solution is complete. The solution is sterilized by filtration through an earthenware or porous stone filter and filled into ampoules. Each cubic centimeter of the solution thus obtained contains 25% by weight or 250 mg. of chloramphenicol. This solution is chemically and physically stable for long periods of time. Upon dilution with water, normal saline, isotonic glucose solution or plasma, no cloudiness or crystal formation takes place. It is relatively non-toxic and can be safely administered intravenously to humans for at least six days in dosages of as high as 2 cc. per day.

EXAMPLE 2.

10 g. of optically racemic chloramphenicol is added to 32 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl acetamide and distilled water at room temperature. The mixture is shaken until solution is complete and sterilized by filtration through a porous stone filter. The solution thus obtained contains 25% racemic chloramphenicol by weight (250 mg./cc.) and is suitable for intravenous administration to humans. Upon dilution of the solution with water, normal saline, isotonic glucose solution or plasma, the solution remains perfectly clear. The undiluted preparation is both chemically and physically stable for long periods of time.

EXAMPLE 3.

26.6 g. of chloramphenicol is added to 20 cc. of N,N-dimethyl acetamide and the mixture shaken until solution is complete. The solution thus obtained after sterilization by filtration through a porous stone filter is suitable for intravenous administration or for use as a concentrate to prepare more dilute solutions for this purpose. The solution is stable in its undiluted form and also upon dilution with water, normal saline, etc. It contains about 645 mg. of chloramphenicol per cc.

EXAMPLE 4.

10 g. of chloramphenicol is added to 22 cc. of a solvent mixture composed of 3 volumes of N,N-dimethyl formamide and 1 volume of isotonic saline. The mixture is shaken until solution is complete, sterilized by filtration through a porous stone filter and filled into ampoules. The solution thus obtained contains 33.3% by weight or 333 mg./cc. of chloramphenicol. It is suitable for intravenous administration and possesses the same properties as the solutions of the preceding examples.

EXAMPLE 5.

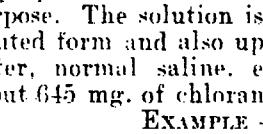
10 g. of chloramphenicol is added to 35 cc. of a solvent mixture composed of equal volumes of N,N-diethyl acetamide and distilled water. The mixture is shaken until solution is complete and then 1 g. of glucose added. The mixture is shaken until the glucose is dissolved and then made up to a volume of 50 cc. by the addition of the amide solvent mixture. The clear solution is sterilized by filtration through an earthenware filter and filled into ampoules. The solution thus obtained is suitable for intravenous administration. It contains 20% by weight or 200 mg./cc. of chloramphenicol and is both physically and chemically stable. The solution can be diluted with any amount of water without causing the chloramphenicol to separate from the solution.

EXAMPLE 6.

10 g. of chloramphenicol is added to 32 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl propionamide and distilled water and the resulting mixture shaken at room temperature until solution is complete. The solution is sterilized by filtration through a porous stone filter and filled into ampoules. This solution is suitable for intravenous administration and contains 25% by weight or 250 mg./cc of chloramphenicol. The chloramphenicol present in the solution does not crystallize out on standing or upon dilution of the solution with water, normal saline, plasma or isotonic glucose solution.

What we claim is:—

1. A clear, stable, liquid therapeutic composition comprising chloramphenicol or optically racemic chloramphenicol dissolved in a water-miscible amide or an aqueous solution containing at least 30% by volume of the water-miscible amide, said amide having the formula,



where R and R_1 are hydrogen or alkyl radicals containing 1 or 2 carbon atoms and R_2 is an alkyl radical containing 1 or 2 carbon atoms.

2. A composition as claimed in Claim 1 wherein the water-miscible amide is a tertiary amide.

3. A composition as claimed in Claims 1 and 2 wherein the water-miscible amide is N,N-dimethyl acetamide.

The invention is illustrated further by the following examples.

EXAMPLE 1.

25 g. of chloramphenicol is added to 80 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl acetamide and distilled water at room temperature and the mixture stirred or shaken until solution is complete. The solution is sterilized by filtration through an earthenware or porous stone filter and filled into ampoules. Each cubic centimeter of the solution thus obtained contains 25% by weight or 250 mg. of chloramphenicol. This solution is chemically and physically stable for long periods of time. Upon dilution with water, normal saline, isotonic glucose solution or plasma, no cloudiness or crystal formation takes place. It is relatively non-toxic and can be safely administered intravenously to humans for at least six days in dosages of as high as 2 cc. per day.

EXAMPLE 2.

10 g. of optically racemic chloramphenicol is added to 32 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl acetamide and distilled water at room temperature. The mixture is shaken until solution is complete and sterilized by filtration through a porous stone filter. The solution thus obtained contains 25% racemic chloramphenicol by weight (250 mg./cc.) and is suitable for intravenous administration to humans. Upon dilution of the solution with water, normal saline, isotonic glucose solution or plasma, the solution remains perfectly clear. The undiluted preparation is both chemically and physically stable for long periods of time.

EXAMPLE 3.

26.6 g. of chloramphenicol is added to 20 cc. of N,N-dimethyl acetamide and the mixture shaken until solution is complete. The solution thus obtained after sterilization by filtration through a porous stone filter is suitable for intravenous administration or for use as a concentrate to prepare more dilute solutions for this purpose. The solution is stable in its undiluted form and also upon dilution with water, normal saline, etc. It contains about 645 mg. of chloramphenicol per cc.

EXAMPLE 4.

10 g. of chloramphenicol is added to 22 cc. of a solvent mixture composed of 3 volumes of N,N-dimethyl formamide and 1 volume of isotonic saline. The mixture is shaken until solution is complete, sterilized by filtration through a porous stone filter and filled into ampoules. The solution thus obtained contains 33.3% by weight or 333 mg./cc. of chloramphenicol. It is suitable for intravenous administration and possesses the same properties as the solutions of the preceding examples.

EXAMPLE 5.

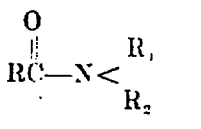
10 g. of chloramphenicol is added to 35 cc. of a solvent mixture composed of equal volumes of N,N-diethyl acetamide and distilled water. The mixture is shaken until solution is complete and then 1 g. of glucose added. The mixture is shaken until the glucose is dissolved and then made up to a volume of 50 cc. by the addition of the amide solvent mixture. The clear solution is sterilized by filtration through an earthenware filter and filled into ampoules. The solution thus obtained is suitable for intravenous administration. It contains 20% by weight or 200 mg./cc. of chloramphenicol and is both physically and chemically stable. The solution can be diluted with any amount of water without causing the chloramphenicol to separate from the solution.

EXAMPLE 6.

10 g. of chloramphenicol is added to 32 cc. of a solvent mixture composed of equal volumes of N,N-dimethyl propionamide and distilled water and the resulting mixture shaken at room temperature until solution is complete. The solution is sterilized by filtration through a porous stone filter and filled into ampoules. This solution is suitable for intravenous administration and contains 25% by weight or 250 mg./cc of chloramphenicol. The chloramphenicol present in the solution does not crystallize out on standing or upon dilution of the solution with water, normal saline, plasma or isotonic glucose solution.

What we claim is:—

1. A clear, stable, liquid therapeutic composition comprising chloramphenicol or optically racemic chloramphenicol dissolved in a water-miscible amide or an aqueous solution containing at least 30% by volume of the water-miscible amide, said amide having the formula.



where R and R_1 are hydrogen or alkyl radicals containing 1 or 2 carbon atoms and R_2 is an alkyl radical containing 1 or 2 carbon atoms.

2. A composition as claimed in Claim 1 wherein the water-miscible amide is a tertiary amide.

3. A composition as claimed in Claims 1 and 2 wherein the water-miscible amide is N,N-dimethyl acetamide.

* C L M S *

4. A composition as claimed in Claims 1 and 2 wherein the water-miscible amide is N,N-dimethyl formamide.

5. Process for preparing a clear, stable, liquid therapeutic composition which comprises dissolving chloramphenicol or optically racemic chloramphenicol in a water-miscible amide or an aqueous solution containing at least 30% by volume of the water-miscible amide, said amide having the formula,

$$RC(=O)-N<^{R_1}_{R_2}$$

where R and R_1 are hydrogen or alkyl radicals containing 1 or 2 carbon atoms and R_2 is an alkyl radical containing 1 or 2 carbon atoms.

6. Process according to Claim 5 wherein the water-miscible amide is a tertiary amide.

7. Process according to Claims 5 and 6 wherein the water-miscible amide is N,N-dimethyl acetamide.

8. Process according to Claims 5 and 6 wherein the water-miscible amide is N,N-dimethyl formamide.

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